REMARKS

The Official Action dated November 10, 2011 has been carefully considered. This Amendment and supporting Remarks are made further in view of a telephone interview held between Applicants and Examiner Gross on January 9, 2012. Applicants wish to thank Examiner Gross for his time and comments. By present Amendment, claim 1 is amended to more clearly define the detectable protecting group in accordance with the invention as defined by the pending claims. Support for this amendment is found, e.g. at page 6, paragraph [0022] – [0025] bridging to page 7. Since no new matter is implicated, entry is believed in order and is respectfully requested.

Claims 1-3, 13, and 15-22 remain pending and under examination.

35 USC §102

Claims 1-2, 13, and 15-22 remain rejected under 35 U.S.C. 102(b) as being anticipated by Agris (US 2002/0045167, of record) ("Agris"). Specifically the Examiner asserts that Agris teaches, throughout the document and especially the abstract and paragraphs 0002-0006 and Figure 11, antibodies specific for oligonucleotide protecting groups applied toward detecting incomplete deprotection on microarrays. According to the Examiner, Agris suggests the antibodies may be used on chips such as developed by Fodor etc., which are made by synthesizing a plurality of biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the biopolymer array is complete, as set forth in claim 1a. The Examiner states that in Figure 8, Agris takes a step to cleave detectable protecting groups such as Bz and ipr-Pac, as set forth in claim 1b; with said antibodies, and to determine the degree of

deprotection by detecting any of Bz and ipr-Pac remaining on an array after cleavage, as set forth in claim 1c; "and re-deprotect until the detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, as set forth in claim 1d." According to the Examiner, antibody binding does not necessarily destroy the oligonucleotides as set forth in the second wherein clause of claim 1. In paragraph 0037 Agris indicates the method may be used with fluorescent protecting groups such as fluorenylmethoxycarbonyl, allegedly reading on claim 2, and that the oligonucleotide reads on the nucleic acid (elected species) of claim 13. The Examiner further asserts that Agris teaches various protected monomeric building blocks in paragraphs 0035-0077 and in particular uses (5'-dimethoxytrityl-N-pehnoxyacetyl-2'-deoxyAdenosine, 3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phoshoramidite in paragraph 0177, which reads on claims 15-22, formula I when R1 is DMT; R2 is H; B is adenine; R6 is a 2 cyanoethyl phosphoramidite; L is –C(O)-R, reading on claims 15-22.

In response to Applicants' previous argument that Agris fails to teach step (d) of claim 1, "repeating steps (b) and (c) until the detectable protecting groups are no longer detected, indicating that complete deprotection is achieved," the Examiner points to Figure 8:

> Fig. 8 shows a blind study **demonstrating the detection of remaining protecting groups** in commercial samples. dA-dC oligos were analyzed with anti-Bz mAb (A) and dG-dT oligos were analyzed with anti-ipr-Pac mAb (B). The oligo dA-dC samples from companies #2 and #6 were tested in higher amounts to confirm the presence of the Bz protecting group (C). In addition, **the samples were treated to remove the remaining protecting groups using a standard protocol.** The oligo dG-dT samples were assayed for the ipr-Pac protecting groups (D). **The samples were re-treated to remove remaining protecting groups and re-analyzed as in (C).** Emphasis added.

Such as shown in Figure 8c right panel columns samples #6* and #2* were re-deprotected (re-treated) until such time as a spot is not detected (i.e. anti-Bz and anti-ipr-Pac mAbs do not bind indicating complete deprotection has been achieved).

The paragraph bridging pages 8-9 of the remarks asserts using the antibodies of Agris would impose degrees of complexity on the synthetic protocol with regard to non-specific binding of fluorescently labeled protecting group antibodies of Agris et al.

In the telephone interview held on January 9, 2012, Applicants made the point that Agris relies on detection of protecting groups by detection of antibodies which bind to protected oligos, but not to deprotected oligos, and does not actually teach on-chip quality control / deprotection with retention of the utility of the chip, since presence of the antibody is determined via immunoassay which requires removal of at least a sample of the array from the chip. The Examiner agreed that where Agris teaches repeating deprotection, it is on commercial samples of oligonucleotides, and where Agris teaches on-chip quality control, the tested oligos are consumed by the assay and a single round of deprotection is tested. The Examiner responded that the limitation is nonetheless taught in the same reference and one can assume that what works with samples could work with chip-bound arrays.

The Examiner further argued that Agris teaches "detectable protecting groups" by virtue of the fact that the protecting groups are detected. The term "detectable" is not inherently limited by operation or functionality, but has plain meaning that governs the novelty analysis. Both parties agreed that more clearly defining the nature of the "detectable protecting group" would establish novelty over Agris and advance prosecution.

As amended, claim 1 is directed to A quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array, the method comprising (a) synthesizing a plurality of biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups

remain coupled until synthesis of the biopolymer array is complete, and wherein the detectable protecting groups are selected from fluorescent groups, radioactively protectable groups, electrochemically protectable groups, and UV or IR protecting groups; (b) taking one or more steps to cleave the detectable protecting groups, (c) determining a degree of deprotection by detecting any of the detectable protecting groups remaining on the array after cleavage, and (d) repeating steps (b) and (c) until the detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip and wherein the synthesized biopolymer are not destroyed by practice of the quality control method.

Significantly, the instant claim requires that the detectable protecting group be selected from a circumscribed list, all of which may be detected without subjecting the chip bound array to an assay which requires removal/consumption of some portion of the array for analysis. Agris fails to teach detectable protecting groups which are detectable by any means other than by assay to detect an antibody specifically constructed by Agris to bind to organic protecting groups. Agris does not teach labeling of the assay for direct detection on the array; rather, Agris teaches any suitable assay exemplified as heterogeneous and homogeneous immunoassay.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986).To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). Agris fails to teach "detectable protecting groups" selected from fluorescent

groups, radioactively protectable groups, electrochemically protectable groups, and UV or IR protecting groups. The "detectability" of the Agris protecting groups is entirely dependent upon the presence of the specific antibody bound thereto. Agri fails to teach or suggest any other mechanism for detecting a protecting group.

Hence, claims 1-2, 13, and 15-22 are novel under 35 U.S.C. §102 over Agris. Reconsideration is respectfully requested.

35 USC §103

Claims 1-2, 13, 15-22 and 3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Agris (US 2002/0045167, of record) in view of Nagaich et al (1989 Nucleic Acids Research 17:5125-5134). Agris is relied on as set forth above. The Examiner notes that Agris does not teach stilbene protecting groups, such as set forth in claim 3.

Nagaich is applied for teaching throughout the document and especially Figure 1, stilbene protecting groups (elected species) for cytidine, adenine and guanine nucleosides reading on claim 3. According to the Examiner it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to utilize the stilbene protecting groups of Nagaich in making microarrays and analysis of deprotection thereof in the manner of Agris.

According to the Examiner, one of ordinary skill in the art would have been motivated to utilize the stilbene protecting groups of Nagaich in making microarrays and analysis of deprotection thereof in the manner of Agris for the advantages of (i) stability of the monomers; (ii) milder conditions for deprotection resulting in negligible side products during synthesis; and (iii) above all greater hydrophobicity, as explicitly noted by Nagaich in last sentence of the abstract.

One of ordinary skill in the art would have had a reasonable expectation of success in applying the stilbene protecting groups toward preparing and analyzing biochips in the manner of Agris since each reference is directly concerned with nucleotide exocyclic amine protection. Thus, according to the Examiner, the teachings of Nagaich et al fall squarely in the scope of technology of interest to Agris.

This rejection is traversed and reconsideration is respectfully requested.

The instant invention provides a simple yet elegant method for assessing a level of deprotection, and for assuring complete deprotection, of array-bound oligonucleotides immediately upon completion of synthesis on the array, and without destroying or consuming any portion of the array. According to the instant invention, during synthesis the oligos are formed with nucleotide building blocks having detectable protecting groups coupled directly to amino groups of the nucleotides. The detectable protecting groups remain coupled until synthesis of the biopolymer array is complete. After steps to remove the protecting groups, the detectable protecting groups are thereafter detectable without any additional processing. That is, they are directly detectable.

Agris, on the other hand, is directed to novel antibodies which bind to organic protecting groups when they are covalently bound to an oligonucleotide, but not when they have been removed. Hence, by detecting the antibody, the technician detects remaining protecting groups. However, Agris teaches that detecting the antibody is via immunoassay. In disclosure relating to directly detectable groups, such as fluorescent groups and the like, Agris suggests that the antibody, not the protecting group, is bound to the detecting group, and Agris teaches that the selection of detecting group is based "upon the immunoassay format in which the antibody is used" ([0081]). Purification is disclosed as a method utilizing affinity purification to separate the

fully deprotected oligonucleotides from those having bound antibody, typically by immobilization on a solid support ([0086]). In the only disclosure in which Agris suggests purification by repeated deprotection and detection steps until full deprotection, Agris tests commercial samples of oligonucleotides, not on-chip arrays.

In disclosure relating specifically to on-chip deprotection, immunoassay is employed to achieve the detecting ([0161]). With respect to "repeated" steps of detection and deprotection, Agris specifically teaches that a different antibody would be used on each repetition ([0162], first sentence), and specifically teaches that the reason is so that "a plurality of different protecting groups which may be present on oligonucleotides in the array may be detected," ([0162]) and NOT to complete the deprotection to the point of purification. In fact, Agris teaches that the result of assessing deprotection on a chip is not to achieve complete deprotection, but to create an indicia of insufficient deprotection which will enable the end user to statistically correct for the deficiency ([0164]-[0166]).

The Examiner has repeatedly insisted that Agris guides the POSITA to the instant invention by taking snippets of disclosure out of context and piecing it together, except that the construction of the instant invention actually uses the guidance provided by the instant specification. For example, while Agris may disclose fluorescent groups among a long list of protecting groups, Agris never suggests any other means of detecting protecting groups other than by utilization of the novel antibody, which Agris teaches as detectable by immunoassay. In contexts where Agris teaches repeated deprotection, Agris teaches methods which consume portions of the oligonucleotide sample. In contexts where Agris teaches deprotection on an array, Agris restricts repeated steps as based on a need to detect different protecting groups with different antibodies, and the result is not complete deprotection on the array, rather, the result is

provision of a statistical indicia so that the end user may correct data for the insufficient deprotection. Clearly Agri contemplates an entirely different solution to the chip quality problem addressed and solved by both.

The secondary reference Nagaich merely teaches what Applicants admit is known in the art – stilbene protecting groups for cytidine, adenine and guanine nucleosides. Nagaich does not, however, recognize or employ them for utility in quality control methods for ensuring complete deprotection of oligonucleotides synthesized on a chip. Nagaich does not overcome the deficiencies of the primary reference.

Hence, claims **1-2, 13, 15-22 and 3** are nonobvious and patentable under 35 U.S.C. 103 over Agris in view of Nagaich. Reconsideration is respectfully requested.

Conclusion

Applicants submit that the foregoing is a complete and persuasive response to the rejections set forth in the office action dated November 10, 2012. Nonetheless if the Examiner perceives any remaining issues which may be readily resolved, he is urged to contact Applicants through their attorney listed below. Otherwise reconsideration and allowance are earnestly solicited.

Sincerely,

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